REMARKS/ARGUMENTS

The Present Invention

The present invention pertains to compositions comprising a dual specificity lymphocyte or a population thereof and a method of preparing the same.

The Pending Claims

Claims 1, 4, 7, 8, 10, 40, 41, 44-46, 52-61, 71-76, 79-93 are pending.

Discussion of the Amendments to the Claims

Claims 11, 47-51, 77, and 78 have been cancelled. Claims 1 and 72 have been amended to recite the claim limitations of claims 77 and 78, respectively. Specifically, the compositions of claims 1 and 72 now include the cell that is allogeneic to the T lymphocytes. Claims 40 and 71 have been amended likewise. Claim 71 has been further amended to be directed to a composition. Claims 79 and 81 have been amended to change "at least one of the T lymphocytes" to "an individual or subpopulation of T lymphocytes" which is supported by the specification at page 17, paragraph 53, as discussed herein. Claims 79 and 81 have been further amended to recite "T lymphocytes" as opposed to "T-cells" in line 5 of each claim. Claims 80 and 82 have been amended in like fashion in line 2 of each claim. The preamble of each of claims 80 and 82 has been further amended to recite "The composition of claim..."

Claims 83-93 have been added and are supported by the instant specification as follows:

Claim	**Specification**
83	Paragraphs 81 and 82
84 and 88	Paragraph 79, line 9
85 and 89	Paragraph 79, line 8
86 and 90	Paragraph 79 and Table 5
87 and 91	Paragraphs 81 and 82
92 and 93	Paragraphs 81 and 82

Discussion of the New Matter Rejection

The Office maintains the rejection of claims 46, 50, 56, and 58, and newly rejects claims 75 and 79-82, under Section 112, first paragraph, as allegedly failing to comply with the written description requirement. The rejection is traversed for the reasons set forth below.

Specifically, the Office contends that an endogenous receptor reactive with a splenocyte is new matter, since the specification does not teach that the dual specificity T lymphocytes administered to mice in Example 5 were reactive to allogeneic splenocytes. The Office alleges that the Declaration of Dr. Patrick Hwu is not persuasive because it is possible that the mice became tumor-free "simply because the T cells had a TCR specific for the tumor."

If the mice became tumor-free due to the administration of T cells having a T cell receptor specific for the tumor, then one would expect that mice that were administered non-transduced T lymphocytes would become tumor-free. This was not the case, however. As shown in Figure 5, the percent of tumor-free mice that were administered non-transduced T lymphocytes (labeled as "NT") was zero. Thus, it is not possible that the mice that were administered transduced T lymphocytes and immunized with allogeneic splenocytes became tumor-free simply because the T cells had a T cell receptor specific for the tumor, as the Office suggested.

As stated in paragraph 3 of the Declaration of Dr. Patrick Hwu (submitted on March 23, 2005), the fact that the tumor-bearing mice became tumor-free upon injection with both allogeneic splenocytes and dual specificity T-cells shows that the allogeneic splenocytes reacted with the endogenous T-cell receptors of the dual specificity T-cells. Also, the specification on page 30, last line through page 31, line 4, states that "Figure 5 shows that *in vivo* immunization with allogeneic splenocytes from donor mice, in combination with administration of dual specificity T cells protected mice much more significantly than T cells alone."

The Office asserts that "[the specification] teaches 'dual specificity allogeneic/Mov-γ T cells' but does not teach that the 'dual specificity' was to splenocytes." It appears that the Office requires that the specification explicitly describes the dual specificity T lymphocytes as being reactive with the allogeneic splenocytes. However, to comply with the written description requirement of 35 USC 112, paragraph 1, each claim limitation must be expressly, *implicitly, or inherently* supported by the originally filed disclosure. MPEP 2163.05. *Ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112. *Fujikawa v. Wattansin* 93 F.3d 1559, 1570, 39 USPQ F.2d 1895, 1904 (Fed. Cir. 1996).

In the instant case, the specification implicitly and inherently supports T lymphocytes comprising a chimeric receptor reactive with a tumor antigen and an endogenous receptor reactive with an allogeneic splenocyte, such that, upon reading Example 5, inclusive of Figure 5, and the Declaration of Dr. Patrick Hwu, one of ordinary skill in the art would recognize that the mice became tumor-free because the dual specificity T lymphocytes that were administered to the mice were reactive with the allogeneic splenocytes that were also administered to the mice. In view of the foregoing, dual specificity T lymphocytes comprising a chimeric receptor reactive with a tumor antigen and an endogenous receptor reactive to an allogeneic splenocyte is not new matter and, thus, the written description requirement has been satisfied.

The Office also rejects claims 79 and 81 for reciting "exposed to a cell that is allogeneic to at least one of the T lymphocytes of the population under conditions which expand and activate the T lymphocytes." The Office alleges that "at least one of the T lymphocytes" does not have support in the specification on pages 31 and 32.

Claims 79 and 81 have been amended to recite "wherein the population of T lymphocytes has been exposed to a cell that is allogeneic to an individual or subpopulation of T lymphocytes of the population under conditions which expand and activate the individual or subpopulation of T lymphocytes." Support for the amended phrase is found in the instant specification at page 17, paragraph 53, which states that "the specific expansion step amplifies *an individual or a subpopulation of T cells* whose endogenous T cell receptor is directed to the strong antigen(s) used to expand the T cells." Therefore, the new matter rejection is obviated in view of the amendments to claims 79 and 81.

The Office further contends that the recitation of "substantially consists of" in claims 80 and 82 is new matter. Claims 80 and 82 have been amended to recite "consists essentially of" in lieu of "substantially consists of." Support for the population consisting essentially of T lymphocytes reactive with the cells that is allogeneic to the T lymphocytes is found in the instant specification at, for instance, paragraphs 81 and 82. Therefore, the new matter rejection is obviated in view of the amendments to claims 79 and 81.

In view of the foregoing, the instantly pending claims do not contain new matter and, thus, meet the written description requirement of Section 112, first paragraph. Applicants respectfully request that the new matter rejection be withdrawn.

Discussion of the Anticipation Rejection

The Office has maintained the rejection of claims 1, 3, 4, 7, 8, 10, 11, 40, 44-61, and 71, and newly rejects claims 72-78, under Section 102 (e) as allegedly inherently anticipated by U.S. Patent 5,830,755 (herein the '755 patent). Claims 1, 3, 7, 8, 11, 40, 41, 45-47, 50, 52, 56, 58, 61, and 71 remain rejected, and claims 75-82 are newly rejected, as allegedly anticipated by U.S. Patent 6,407,221 (herein the '221 patent). Claims 1, 3, 7, 8, 11, 40, 41, 45-47, 50, 52, 56, 58, 61, and 71 remain rejected, and claims 72 and 75-82 are newly rejected, as allegedly anticipated by U.S. Patent 5,359,046 (herein the '046 patent). The rejections are traversed for the reasons set forth below.

I. The '755 Patent

The 102 (e) rejection based on the second and third interpretations of the '755 patent is maintained.

In the second interpretation, the Office argues that the endogenous receptor that is reactive to a cell that is allogeneic to the lymphocyte is inherent to the T lymphocytes disclosed in the '755 patent. The Office relies on the teachings of Shilyansky et al., *PNAS* 91: 2829-2833 (1994); Nishimura et al., *J. Immunotherapy* 16: 85-94 (1994); Wang et al., *J. Immunology* 154: 1797-1903 (1995); and Cole et al., *Cancer Res.* 57: 5320-5327 (1997), which allegedly describe the variable and diverse nature of TIL T cell receptors.

However, the fact that the nature of T cell receptors are variable and diverse does not necessarily mean that a given population of T lymphocytes has a T lymphocyte comprising a T cell receptor reactive with an allogeneic cell. Therefore, the Office has not provided evidence, by way of published references, that demonstrates that the cells *necessarily* have the endogenous receptor as claimed. See MPEP 2112, Section IV. Since inherency may not be established by probabilities or possibilities, the rejection is improper on this basis alone. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 20 USPQ2d 1746 (Fed. Cir. 1991).

Even if the TIL described in the '755 patent necessarily comprised a T lymphocyte comprising a T cell receptor reactive with an allogeneic cell, which they do not, the '755 patent at column 37, lines 63-65, discloses that the native antigen of the TIL is MC38 tumor cells. Therefore, the endogenous T cell receptor of the TIL of the '755 patent cannot be

reactive to an allogeneic cell, since the '755 patent teaches that the T cell receptor is reactive to MC38 tumor cells.

In view of the foregoing, the second interpretation of the '755 patent cannot be said to support the inherent anticipation rejection.

In the third interpretation, the Office contends that the TIL described in the '755 patent inherently have an endogenous T cell receptor that reacts with an allogeneic cell, wherein the allogeneic cell has been transfected to express FBP, since the TIL were stimulated with FBP. As stated above, the '755 patent teaches that the T cell receptor is reactive to MC38 tumor cells, and, therefore, it cannot be true that the TIL described in the '755 patent inherently have an endogenous T cell receptor that reacts with an allogeneic cell.

In view of the foregoing, the third interpretation cannot be said to support the inherent anticipation rejection.

Therefore, the claims of the instant application are not anticipated, either inherently or explicitly, by the '755 patent. Applicants, therefore, request that the 102 (e) rejection based on the '755 patent be withdrawn.

II. The '221 and '046 Patents

The Office argues that the lymphocytes taught in the '221 and '046 patents anticipate the claimed dual specificity lymphocytes, contending that the lymphocytes expressed a chimeric receptor reactive with a tumor antigen, since the chimeric receptor was reactive to an antigen that was recombinantly expressed by a tumor cell. The Office further alleges that these lymphocytes expressing the chimeric receptor inherently expressed a second receptor that is an endogenous T-cell receptor reactive with the allogeneic cell line, since the lymphocytes were allegedly stimulated with 293 cells.

The '221 and '046 patents teach T lymphocytes transduced with a gene encoding a chimeric receptor reactive with the HIV antigen, gp160, which is subsequently processed into gp120. As stated in the previous Reply to Office Action submitted on March 23, 2005, "tumor antigen" is defined in the instant application on page 13, lines 8-15 of paragraph 0046, as a *molecule that can be used to target therapy against a tumor* and includes those antigens only found on tumor cells (i.e., tumor specific), those which are expressed on tumor cells and on limited normal tissues, and those which are over-expressed on tumor cells compared to the expression on a wide variety of normal tissues (i.e., over-expressed antigens). Also, the

specification at page 13, lines 15-18, lists several examples of over-expressed tumor antigens, all of which are known to be over-expressed on a tumor *in vivo* and, unlike the gp120 protein of the '221 and '046 patents, are not *caused to be expressed* by a tumor cell. Therefore, because the gp120 protein is not a molecule that can be used to target therapy against a tumor *in vivo*, this protein cannot be considered as a tumor antigen as defined by the instant application.

Further, one of ordinary skill in the art does not consider gp120 as a tumor antigen. See Roberts et al., *Blood* 84: 2878-2889 (1994), a copy of which is enclosed herewith, which describes T cells expressing chimeric receptors to "HIV antigens," namely, gp120.

Even if gp120 could be considered a tumor antigen, which it cannot, the Office has not provided evidence, by way of published references, that demonstrates that the TIL disclosed by the '221 and '046 patents *necessarily* have the endogenous receptor as claimed. By pointing to Shilyansky et al., Nishimura et al., Wang et al., and Cole et al., the Office has merely demonstrated that the nature of the TIL T cell receptors is variable and diverse. Therefore, the rejection is improper.

The Office alleges that the endogenous T-cell receptor reactive with an allogeneic cell is inherent to the T lymphocytes, since the lymphocytes were allegedly stimulated with 293 cells. However, the '221 patent does not teach that the 293 cells stimulated the T lymphocytes. In fact, the '221 patent at column 31, line 51, teaches that the 293 cells served as transient viral producers. The Office has provided no evidence for the allegation that the 293 cells served as allogeneic cells to which the endogenous T cell receptor of the T lymphocytes is reactive.

In view of the foregoing, Applicants respectfully maintain that neither the '221 or '046 patents inherently anticipate the claimed invention.

However, in order to advance prosecution and not in acquiescence of the rejection, claim 11 has been cancelled, while claims 1, 40, 71, and 72 have been amended to be directed to a composition comprising (A) a T lymphocyte comprising (i) a recombinant chimeric receptor or a recombinant T cell receptor, either of which are reactive with a tumor antigen, and (ii) an endogenous T cell receptor reactive with a cell that is allogeneic to the lymphocyte, and (B) the cell that is allogeneic to the T lymphocyte. As a result of such claim amendments, all of the instantly pending product claims are directed to a composition comprising the dual specific T lymphocyte, or a population thereof, in combination with the

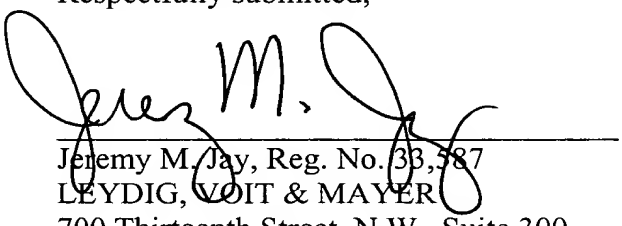
allogeneic cell. Such compositions are neither inherently nor explicitly disclosed by the prior art.

In view of the foregoing, none of the instantly pending claims are taught by the prior art. Therefore, it is hereby requested that the rejection under 102 (e) be withdrawn.

Conclusion

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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